Journal of the American College of Cardiology Vol. 59, No. 13, 2012

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.12.020

# Impact of QRS Duration and Morphology on the Risk of Sudden Cardiac Death in Asymptomatic Patients With Aortic Stenosis

## The SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) Study

Anders M. Greve, MD,* Eva Gerdts, MD, PhD,† Kurt Boman, MD, PhD,‡ Christa Gohlke-Baerwolf, MD,§ Anne B. Rossebø, MD,‖ Richard B. Devereux, MD,¶ Lars Køber, MD,* Simon Ray, MD,# Ronnie Willenheimer, MD, PhD,** Kristian Wachtell, MD, PhD*††

*Copenhagen and Gentofte, Denmark; Bergen and Oslo, Norway; Skelleftå and Malmö, Sweden; Bad Krozingen, Germany; New York, New York; and Manchester, United Kingdom*

**Objectives** The aim of the study was to examine the predictive value of QRS duration and morphology during watchful waiting in asymptomatic patients with aortic stenosis (AS).

**Background** QRS duration and morphology are associated with poor prognosis in many different populations, but the predictive value, particularly of the risk of sudden cardiac death (SCD), in asymptomatic patients with AS has not been well studied.

**Methods** Data were obtained in asymptomatic AS patients randomized to simvastatin/ezetimibe combination versus placebo in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study. The impact of QRS duration, evaluated as a categorical variable of <85 ms versus 85 to 99 ms and ≥100 ms (excluding bundle branch block [BBB]) and QRS morphology in those with BBB, on cardiovascular morbidity and mortality was assessed by adjusting for clinical and echocardiographic covariates.

**Results** QRS data were available in 1,542 patients who were followed for a mean of 4.3 ± 0.8 years (6,631 patient-years of follow-up). There were 68 cardiovascular deaths (4.6%), including 27 SCDs (1.8%). QRS duration was <85 ms in 900 patients (58.4%), 85 to 99 ms in 396 (25.7%), ≥100 ms in those without BBB in 144 (9.3%), and 102 (6.6%) in those with BBB. In multivariable analyses, those with QRS duration ≥100 ms had, compared with those with QRS duration <85 ms, a 5-fold higher risk of SCD (95% confidence interval: 1.8 to 13.7, $p = 0.002$) and a 2.5-fold higher risk of cardiovascular death (95% confidence interval: 1.2 to 5.1, $p = 0.01$).

**Conclusions** QRS duration and morphology in asymptomatic patients with AS are independently associated with a poor prognosis, particularly the risk of SCD. (Simvastatin Ezetimibe in Aortic Stenosis [SEAS]; NCT00092677)
(J Am Coll Cardiol 2012;59:1142–9) © 2012 by the American College of Cardiology Foundation

The increased afterload associated with aortic stenosis (AS) initially induces compensatory left ventricular (LV) hypertrophy and ultimately results in impaired LV systolic function as well as symptoms of heart failure (1). The onset of symptoms or LV systolic dysfunction is generally accepted as adverse signs in initially asymptomatic patients with AS and represents guideline criteria for aortic valve replacement (AVR) (2). The annual risk of sudden cardiac death (SCD)

From the *Department of Medicine B, The Heart Center, Rigshospitalet, Copenhagen, Denmark; †University of Bergen and Haukeland University Hospital, Bergen, Norway; ‡Skelleftå Lasarett and Umeå University, Skelleftå, Sweden; §Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany; ‖Department of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway; ¶Weill Cornell Medical College, New York, New York; #Manchester Academic Health Sciences Centre, Manchester, United Kingdom; **Heart Health Group and Lund University Hospital, Malmö, Sweden; and the ††Gentofte University Hospital, Gentofte, Denmark. The SEAS study was conducted with financial support from Merck & Co, Inc. Drs. Boman, Devereux, Gerdts, Gohlke-Baerwolf, Rossebø, Willenheimer, and Wachtell have received honoraria from Merck & Co., Inc., the funding sponsor of the SEAS study. Dr. Willenheimer received honoraria from AstraZeneca Inc. and Pfizer Inc. Dr. Devereux has served as a consultant to Novartis and Sanofi-Aventis. Dr. Willenheimer has participated in advisory boards and/or received consultancy fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck Serono, MSD, Novartis, Pfizer, Servier, and Vifor. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 27, 2011; revised manuscript received November 29, 2011, accepted December 7, 2011.

is ~0.4% per year in patients who have not yet met current criteria for AVR (3). Therefore, predictors of adverse outcome, and in particular SCD, are of special interest in asymptomatic AS because they may lead to a better selection of patients for AVR, perhaps reducing the risk of adverse outcome and prevention of SCD. In this regard, increased QRS duration is appealing because it has been shown to be associated with LV hypertrophy and the risk of congestive heart failure in the general population as well as the risk of SCD in patients with increased afterload due to hypertension or with impaired LV ejection fraction (4–7). Moreover, it is a low-cost, easily obtainable, and reproducible parameter. Several studies have suggested differing etiologies of left bundle branch block (LBBB), which is associated with LV dysfunction, right bundle branch block (RBBB), often in the absence of overt heart disease, and prolonged QRS duration not meeting the criteria for bundle branch block (BBB) (8). However, the association of QRS duration, especially lesser degrees of QRS prolongation (<120 ms), with the risk of adverse outcome, particularly SCD, and the additive value of QRS morphology, in those with BBB, have not been well studied in asymptomatic patients with AS. Thus, the present study investigated whether: 1) QRS duration in patients without BBB is related to the risk of cardiovascular morbidity and mortality, particularly of SCD; and 2) QRS morphology in those with BBB added prognostic information during long-term follow-up in asymptomatic patients with mild to moderate AS and preserved LV systolic function.

## Methods

**Study population.** The SEAS (Simvastatin Ezetimibe in Aortic Stenosis) study was a multicenter, randomized, double-blind, placebo-controlled study investigating whether intensive lipid-lowering with simvastatin/ezetimibe combination compared with placebo could reduce the need for AVR and the risk of cardiovascular morbidity and mortality in 1,873 patients from ages 45 to 85 years with asymptomatic mild to moderate AS (defined as echocardiographic aortic valve thickening accompanied by a Doppler-measured aortic peak flow velocity ≥2.5 and ≤4.0 m/s and normal systolic LV function). The main outcome including study design, organization, clinical measures, exclusion criteria (most important systolic heart failure, diabetes, and known ischemic heart disease), baseline characteristics, and main outcome were published previously (9,10). This study uses pre-specified analyses of prospectively collected data from the SEAS and the SEAS electrocardiographic substudy to investigate whether QRS duration is independently associated with the risk of SCD, overall cardiovascular death, cardiovascular morbidity, AVR, and all-cause mortality in asymptomatic patients with AS. This study complies with the Declaration of Helsinki, and locally appointed ethics committees approved the research protocol, and informed consent was obtained from all participants.

**Abbreviations and Acronyms**

- **AS** = aortic stenosis
- **AVR** = aortic valve replacement
- **BBB** = bundle branch block
- **CI** = confidence interval
- **HR** = hazard ratio
- **LBBB** = left bundle branch block
- **LV** = left ventricular
- **RBBB** = right bundle branch block
- **SCD** = sudden cardiac death

**Electrocardiography.** Electrocardiographic study protocol, reading procedures, and reproducibility were published (11). In short, electrocardiograms were recorded at the local study centers at a paper speed of 25 or 50 mm/s, after which they were sent to the central electrocardiogram core laboratory at The Heart Center, Rigshospitalet, Copenhagen, Denmark. A physician, blinded to the randomization and all clinical data, read and transferred all electrocardiograms directly to an electrocardiogram database, using Minnesota codes, in agreement with recent recommendations (12). QRS duration was measured in the lead with the greatest QRS width. Patients were grouped according to: 1) QRS duration <85 ms; 2) QRS duration 85 to 99 ms; 3) QRS duration ≥100 ms (excluding patients with BBB); 4) LBBB; and 5) RBBB with and without left anterior fascicular block.

**Echocardiography.** The echocardiographic study protocol, reading procedures, and reproducibility were published (13). In short, transthoracic echocardiograms were read blinded at the SEAS echocardiography core laboratory at Haukeland University Hospital in Bergen, Norway. The aortic valve area was calculated using the continuity equation, in accordance with recent recommendations (14). Quantitative echocardiography was performed according to American Society of Echocardiography guidelines (15).

**Endpoints.** All endpoints were classified by an endpoint committee blinded to a randomization group with a pre-specified endpoint manual prepared by the SEAS steering committee (9). Specific endpoints were: 1) SCD (defined as either witnessed instantaneous unexpected death occurring without preceding symptoms or nonwitnessed unexpected death, if other causes of death were excluded with reasonable certainty [i.e., patients who had known signs, symptoms, or other fatal disease when last observed] or cardiac death occurring <24 h after onset of cardiac symptoms [e.g., acute pulmonary edema or cardiogenic shock]); 2) cardiovascular death (defined as death caused by complications of myocardial infarction, progressive heart failure, cerebrovascular disease, complications of cardiac surgery or intervention, other cardiac or cardiovascular diseases including SCD as defined previously); 3) AVR (defined as AVR as a single operative procedure or performed in combination with other procedures); 4) hospitalization for incident congestive heart failure (excluding patients after AVR, known heart failure, aortic valve area >1.0 $cm^2$, and/or known heart disease, aside from AS, that could have contributed to the development of heart failure); 5) nonfatal and fatal myocardial infarction (defined as a typical increase and decrease in troponin or creatine kinase–myocardial band

plus at least 1 of the following: ischemic symptoms, ischemic electrocardiographic changes (new pathologic Q waves, ST-segment elevation, ST-segment depression, inversion of T waves in at least 2 leads, and/or percutaneous coronary intervention with significant coronary stenosis/thrombus).

**Statistical analysis.** Data were analyzed using the SAS version 9.1 (SAS Institute, Cary, North Carolina). Continuous data are expressed as mean ± SD and categorical variables as proportions. Continuous variables were normally distributed, except for QRS duration, which was assessed as a categorical variable by assigning indicator variables to QRS duration: 1) <85 ms; 2) 85 to 99 ms; 3) ≥100 ms (excluding patients with BBB); 4) LBBB; and 5) RBBB with and without left anterior fascicular block. Due to suspected different etiology, patients with RBBB were set aside for separate hypothesis-generating analyses. Differences in continuous variables were evaluated by using 1-way ANOVA (with unweighted mean analysis due to unequal sample sizes) and trend tests for categorical variables. To reduce the risk of type I error, pairwise comparisons with a reference group (QRS <85 ms) were adjusted by Dunnett's test for multiple comparisons. The impact of the simvastatin/ezetimibe combination compared with placebo on progression in QRS duration was assessed in a mixed model using repeated measures of annual in-study electrocardiographic re-examinations. QRS duration as a continuous and categorical variable (as defined earlier) satisfied the linear and proportional hazard assumptions for Cox time-to-event modeling. Associations of QRS duration, as a categorical variable, with all cause-mortality and other endpoints (i.e., heart failure, AVR, acute myocardial infarction, SCD, and cardiovascular death) were analyzed by Cox models and by competing risk regression (using death as a competing event), as described by Fine and Gray (16), respectively. The effects are expressed by cause-specific hazard ratio (HR) and 95% confidence interval (CI). Differences in the incidence of SCD and overall cardiovascular death among groups of QRS duration were evaluated by log-rank tests. Multivariable relationships were determined by adjusting for classic risk factors differing among the groups of QRS duration and with significant univariate impact on the investigated outcome, selected from stepwise regression of age, sex, LV ejection fraction, LV mass indexed by body surface area, and estimated glomerular filtration rate ($[ml/min/1.73\ m^2] = 186 \times [\text{serum creatinine } (\mu mol/l) \times 0.011312]^{-1.154} \times [age]^{-0.203} \times [0.742 \text{ if female}]$). Additional measures were taken to avoid overfitting the multivariable models; 1) QRS duration was investigated as covariate with 3 degrees of freedom (as defined), and 2) computerized backward elimination was performed in all models in which QRS duration (as a categorical variable) was a multivariable predictor (with $p < 0.05$ needed to stay in the model). All analyses were checked for the influence of randomized treatment, but this did not alter the results, and the covariate was not included in the final analyses (data not presented). The additive prognostic value of QRS duration was evaluated as described by Pencina et al. (17). Because there is no established score system for SCD in asymptomatic AS, a priori risk categories of SCD were set at <0.9% (expected occurrence in age- and sex-matched U.S. background) (18), 0.9% to 5%, and >5% (during the mean follow-up of 4.3 years). To test whether the impact of QRS duration on SCD was sensitive to the definition of SCD, an additional analysis was performed using a breakdown of SCD with and without preceding symptoms of heart failure or angina in accordance with a modified Hinkle-Thaler classification (19). Proportionality and linearity assumption for all variables in the multivariable models were checked by testing the dependence of their relative risk estimate over time. There were no significant differences in the competing event (noncardiovascular death) among groups of baseline QRS duration and LBBB (data not presented); cumulative incidence plots of SCD and cardiovascular death are therefore given as rates of the investigated endpoint per se. Interaction terms were not included in the models because there was no a priori suspicion of interaction. A 2-tailed p value <0.05 was required for statistical significance.

## Results

**Baseline characteristics.** Baseline electrocardiograms were available for 1,563 patients; QRS duration could be assessed in 1,542, missing values were due to 100% ventricular pacing (n = 10, 0.6%) or poor quality of electrocardiogram (n = 11, 0.7%), with no significant difference in distribution of age, sex, peak aortic jet velocity, and LV mass between patients with and without data for the current study (data not presented). The study population consisted of 942 men (61.1%) and 600 women (38.9%) followed for a mean of 4.3 ± 0.8 years, totaling 6,631 patient-years of follow-up. The mean age was 67.4 ± 9.6 years and the mean peak aortic jet velocity was 3.1 ± 0.5 m/s. Groups with QRS duration <85 ms (n = 900, 58.3%), 85 to 99 ms (n = 396, 25.7%), ≥100 ms without BBB (n = 144, 9.3%), and LBBB (n = 43, 2.8%) differed in the mean LV diameter in diastole and systole, LV posterior wall thickness, intraventricular septal thickness, LV ejection fraction, LV mass/body surface area, heart rate, body mass index, cholesterol levels, and the proportion of women and prevalence of hypertension (Table 1).

**Clinical impact of baseline QRS duration and LBBB.** A total of 140 deaths occurred (9.4%); 68 were categorized as cardiovascular (4.6%) and 27 as SCDs (1.8%, annual rate ~0.4%), 428 patients were referred for AVR (28.9%), 36 experienced incident myocardial infarction (2.4%), and 34 were hospitalized for heart failure before AVR (2.3%). End-of-study cumulative incidences according to QRS duration and LBBB are given in Table 2, and the impact of QRS duration ≥100 ms and LBBB, compared with those with QRS duration <85 ms, in Table 3. The annual rates of SCD and overall cardiovascular death were, respectively, ~0.2% and 0.8% in QRS duration <85 ms, 0.5% and 1.2%

**Table 1** Baseline Demographics and Echocardiographic Characteristics According to QRS Duration and LBBB

| | QRS <85 ms (n = 900) | QRS 85–99 ms (n = 396) | QRS 100–119 ms (n = 144) | LBBB (n = 43) | Overall p Value |
|---|---|---|---|---|---|
| Age, yrs | 67.5 ± 9.5 | 66.5 ± 9.7 | 66.2 ± 10.2 | 71.2 ± 8.1* | <0.01 |
| Male, % | 51.0 | 72.0* | 83.3* | 65.1 | <0.001 |
| Systolic blood pressure, mm Hg | 144.3 ± 20.5 | 146.2 ± 19.5 | 146.8 ± 20.8 | 144.4 ± 21.7 | 0.30 |
| Diastolic blood pressure, mm Hg | 81.9 ± 10.4 | 82.4 ± 10.9 | 82.5 ± 10.2 | 80.0 ± 10.6 | 0.50 |
| History of hypertension, % | 47.4 | 57.3 | 57.6* | 62.8* | <0.001 |
| Heart rate, beats/min | 66.1 ± 11.5 | 64.1 ± 10.2* | 62.1 ± 11.6* | 62.2 ± 9.8 | <0.001 |
| Body mass index, kg/m$^2$ | 26.6 ± 0.55 | 27.2 ± 4.4 | 27.6 ± 4.4 | 27.6 ± 4.0 | 0.04 |
| Peak aortic jet velocity, m/s | 3.08 ± 0.55 | 3.09 ± 0.55 | 3.13 ± 0.52 | 2.97 ± 0.54 | 0.36 |
| Mild aortic stenosis, %† | 47.5 | 46.1 | 37.2 | 57.1 | 0.08 |
| Aortic valve area/BSA, cm/m$^2$ | 0.61 ± 0.19 | 0.61 ± 0.19 | 0.58 ± 0.17 | 0.62 ± 0.23 | 0.30 |
| Sokolow-Lyon voltage, mV | 26.5 ± 0.6 | 27.9 ± 0.9* | 27.9 ± 1.5 | 28.0 ± 2.8 | 0.04 |
| Cornell voltage, mV | 18.3 ± 7.0 | 20.3 ± 7.7* | 23.7 ± 9.3* | 33.5 ± 8.1* | <0.001 |
| Cornell voltage duration product, mV × ms | 1,467.5 ± 44.1 | 1,823.0 ± 67.2* | 2,432.0 ± 111.7* | 4,464.7 ± 202.3* | <0.001 |
| Left anterior fascicular block, % | 4.0 | 9.1* | 25.0* | — | <0.001 |
| QRS axis, ° | 18.8 ± 32.4 | 12.8 ± 36.7* | −0.6 ± 43.1* | −25.0 ± 22.9* | <0.001 |
| Left ventricular mass/BSA, g/m$^2$ | 93.0 ± 25.5 | 106.6 ± 31.4* | 118.3 ± 39.2* | 115.0 ± 35.8* | <0.001 |
| Left ventricular ejection fraction, % | 66.7 ± 8.0 | 64.5 ± 10.0* | 63.1 ± 8.8* | 62.3 ± 8.6* | <0.001 |
| Posterior wall thickness, cm | 0.84 ± 0.17 | 0.89 ± 0.19* | 0.95 ± 0.20* | 0.91 ± 0.17* | <0.001 |
| Left ventricular dimension, cm | 4.92 ± 0.60 | 5.22 ± 0.60* | 5.34 ± 0.70* | 5.22 ± 0.71* | <0.001 |
| Left ventricular dimension in systole, cm | 3.09 ± 0.52 | 3.34 ± 0.55* | 3.49 ± 0.64* | 3.45 ± 0.64* | <0.001 |
| Relative wall thickness , LV posterior wall/LV internal radius | 0.35 ± 0.09 | 0.35 ± 0.09 | 0.36 ± 0.09 | 0.36 ± 0.08 | 0.32 |
| Intraventricular septal thickness, cm | 1.10 ± 0.26 | 1.18 ± 0.29* | 1.24 ± 0.29* | 1.22 ± 0.25* | <0.001 |
| Stroke index, ml/m(height)$^{2.04}$ | 25.9 ± 6.1 | 25.7 ± 6.6 | 25.0 ± 5.8 | 25.1 ± 6.7 | 0.40 |
| Estimated GFR, ml/min/1.73 m$^2$ | 67.6 ± 11.6 | 68.7 ± 12.6 | 71.0 ± 13.6* | 67.3 ± 11.8 | 0.02 |
| High-density lipoprotein cholesterol, mmol/l | 1.54 ± 0.44 | 1.47 ± 0.40* | 1.43 ± 0.43* | 1.50 ± 0.42 | 0.005 |
| Low-density lipoprotein cholesterol, mmol/l | 3.60 ± 0.87 | 3.50 ± 0.90 | 3.40 ± 0.82* | 3.62 ± 0.95 | 0.03 |
| Beta-blockers, % | 48.7 | 49.8 | 55.6 | 58.1 | 0.08 |
| Drugs acting on the renin-angiotensin system, % | 39.3 | 45.7* | 36.8 | 55.8* | 0.11 |
| Diuretics, % | 43.6 | 47.2 | 48.6 | 55.8 | <0.05 |

Values are mean ± SD or %. *p < 0.05 compared with QRS duration <85 ms (Dunnett's test). †Mild = peak aortic jet velocity >2.5 to <3.0 m/s.
BSA = body surface area; GFR = glomerular filtration rate; LBBB = left bundle branch block.

in QRS duration of 85 to 99 ms, 1.3% and 2.3% in QRS duration 100 to 119 ms compared with 0.6% and 1.1% in LBBB. Considering QRS duration as a linear predictor, the risk of SCD increased with ~40% per 10 ms greater QRS width (HR: 1.4; 95% CI: 1.1 to 1.7; p = 0.005). Further analyses excluding patients with LBBB showed that the risk of SCD increased 2.2-fold per 10 ms greater QRS width (HR: 2.2; 95% CI: 1.5 to 3.2; p < 0.001). In multivariable analyses, patients with QRS duration of 100 to 119 ms had, compared with those with QRS duration <85 ms, a 5-fold higher risk of SCD (95% CI: 1.8 to 13.7; p = 0.002) and a 2.5-fold higher risk of cardiovascular death (95% CI: 1.2 to 5.1; p = 0.01). Stratifying the latter analysis by SCDs with preceding symptoms (n = 4, 2 admitted for heart failure in QRS duration <85 ms and 2 diagnosed with angina in QRS duration 100 to 119 ms), patients with QRS duration 100 to 119 ms remained, compared with those with QRS duration <85 ms, at a 4.7-fold higher risk of SCD (95% CI: 1.7 to 13.1; p = 0.003). Cumulative incidences of SCD and cardiovascular death in groups of baseline QRS duration and LBBB are presented in Figures 1 and 2, respectively. Of all the variables included in the multivariable model, longer

**Table 2** End-of-Study Cumulative Incidence of Endpoints According to QRS Duration and LBBB

| | QRS <85 ms (n = 900) | QRS 85–99 ms (n = 396) | QRS 100–119 ms (n = 144) | LBBB (n = 43) | Overall p Value |
|---|---|---|---|---|---|
| Sudden cardiac death | 9 (1.0) | 9 (2.3) | 8 (5.6)* | 1 (2.3) | 0.005 |
| Cardiovascular death | 31 (3.4) | 21 (5.3) | 14 (9.7)* | 2 (4.7) | 0.009 |
| Aortic valve replacement, | 252 (28.0) | 124 (31.3) | 43 (29.9) | 9 (20.9) | 0.28 |
| Heart failure | 18 (2.0) | 7 (1.8) | 6 (4.2) | 3 (7.0)* | 0.07 |
| Myocardial infarction | 21 (2.3) | 8 (2.0) | 5 (3.5) | 2 (4.7) | 0.56 |
| All-cause mortality | 73 (8.1) | 43 (10.9) | 18 (12.5) | 6 (14.0) | 0.12 |

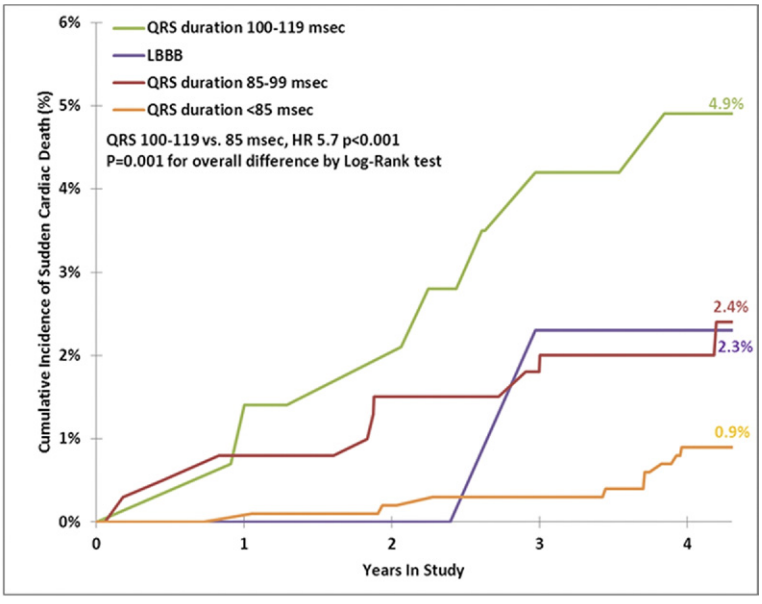
Values are n (%). *p < 0.05 compared with QRS duration <85 ms (competing risk regression).
LBBB = left bundle branch block.

**Table 3** HRs for QRS Duration 100 to 119 ms and LBBB Versus QRS Duration <85 ms

| | QRS Duration 100–119 ms | | | | Left Bundle Branch Block | | | |
|---|---|---|---|---|---|---|---|---|
| Endpoint | Unadjusted HR (95% CI) | p Value | Adjusted HR (95% CI) | p Value | Unadjusted HR (95% CI) | p Value | Adjusted HR (95% CI) | p Value |
| Sudden cardiac death* | 5.7 (2.2–14.9) | <0.001 | 5.0 (1.8–13.7)† | 0.002 | 2.4 (0.3–19.2) | 0.40 | 1.6 (0.2–13.0)† | 0.65 |
| Cardiovascular death* | 3.0 (1.6–5.5) | <0.001 | 2.5 (1.2–5.1)‡ | 0.01 | 1.4 (0.3–6.0) | 0.62 | 0.9 (0.2–3.7)‡ | 0.83 |
| Aortic valve replacement* | 1.2 (0.9–1.6) | 0.29 | 1.0 (0.7–1.4)§ | 0.80 | 0.8 (0.4–1.5) | 0.78 | 0.8 (0.4–1.7)§ | 0.60 |
| Heart failure* | 2.2 (0.9–5.6) | 0.09 | 1.3 (0.4–3.9)‖ | 0.62 | 3.8 (1.1–12.8) | 0.03 | 1.1 (0.2–4.9)‖ | 0.91 |
| Myocardial infarction* | 1.5 (0.6–4.1) | 0.39 | 2.1 (0.7–6.1)† | 0.16 | 2.2 (0.5–9.2) | 0.30 | 1.0 (0.1–7.7)† | 1.00 |
| All-cause mortality* | 1.6 (1.0–2.7) | 0.07 | 1.4 (0.7–2.5)‡ | 0.32 | 1.8 (0.8–4.2) | 0.15 | 0.9 (0.4–2.3)‡ | 0.85 |

Adjusted by covariates with significant univariate impact on investigated outcome: *Reference QRS duration <85 ms. †Age and left ventricular mass indexed by body surface area. ‡Age, left ventricular mass indexed by body surface area, estimated glomerular filtration rate, and left ventricular ejection fraction. §Age, sex, left ventricular mass indexed by body surface area, estimated glomerular filtration rate, left ventricular ejection fraction, and peak aortic jet velocity (did not differ between groups of QRS duration). ‖Age and left ventricular ejection fraction.
CI = confidence interval; HR = hazard ratio; LBBB = left bundle branch block.

QRS duration and older age were the only significant predictors of SCD. Using backward elimination, longer QRS duration ($p = 0.002$ for an overall test of QRS groups, QRS duration of 100 to 119 ms vs. <85 ms, HR: 6.4; 95% CI: 2.5 to 16.7; $p < 0.001$) and older age (HR: 1.06; 95% CI: 1.01 to 1.12; $p = 0.01$) were both independently associated with the risk of SCD. Similarly, in backward elimination of all covariates included in the model with overall cardiovascular death as the outcome, longer QRS duration ($p = 0.03$ for an overall test of QRS groups, QRS duration of 100 to 119 ms vs. <85 ms, HR: 2.8; 95% CI: 1.4 to 5.6; $p = 0.003$), older age (HR: 1.1 per 1 year; 95% CI: 1.1 to 1.1; $p < 0.001$), and lower LV ejection fraction (HR: 1.04 per 1% lower; 95% CI: 1.01 to 1.07; $p = 0.007$) remained as independent predictors. Adding QRS duration as a categorical variable to a model with SCD as an outcome and age and LV mass indexed by body surface area as covariates increased the C index 2.6% (receiver-operating characteristic curve area shifted from 70.4% to 73.0%; $p = 0.02$) and improved net reclassification index by 21.0% ($p = 0.03$). Almost all (92.6%) SCDs occurred before AVR; adding AVR as a time-dependent covariate in a model with age, sex, randomized treatment, and QRS duration did not significantly alter the impact of QRS duration on SCD. In this model, AVR was not associated with a change in the risk of SCD ($p = 0.30$, based on 776 patient-years of




No. at risk

| | | | | | |
|---|---|---|---|---|---|
| QRS <85 msec | 900 | 893 | 876 | 857 | 836 |
| QRS 85-99 msec | 396 | 390 | 380 | 368 | 355 |
| QRS 100-119 msec | 144 | 141 | 137 | 131 | 129 |
| LBBB | 43 | 42 | 42 | 40 | 37 |

**Figure 1** Rate of Sudden Cardiac Death by QRS Group

Cumulative incidence of sudden cardiac death according to baseline QRS duration and left bundle branch block (LBBB) during 4.3 years of follow-up. HR = hazard ratio.

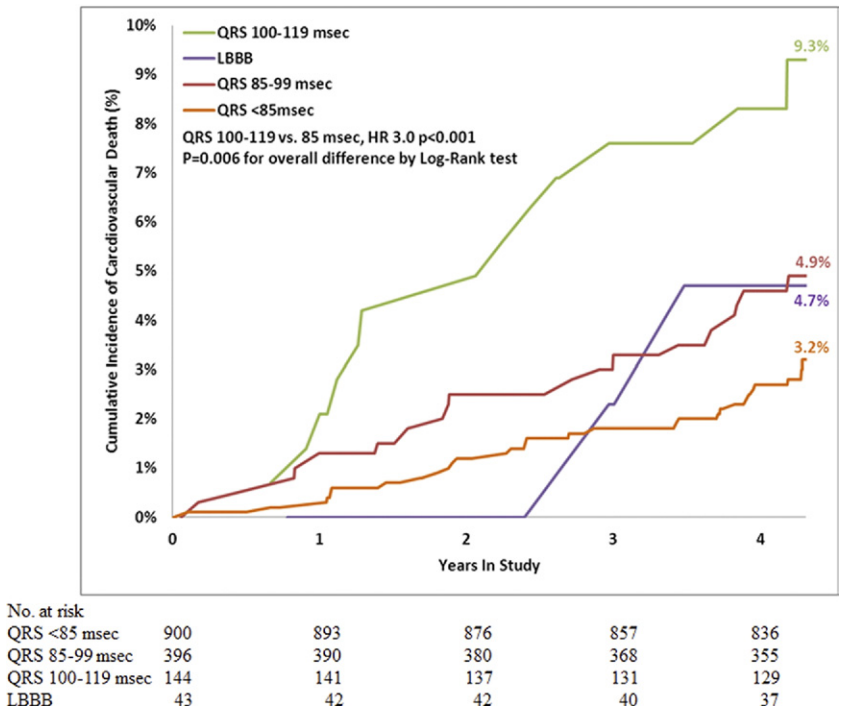



**Figure 2** Rate of Cardiovascular Death by QRS Group

Cumulative incidence of overall cardiovascular death according to baseline QRS duration and LBBB during 4.3 years of follow-up. Abbreviations as in Figure 1.

follow-up after AVR). Similarly, using incident myocardial infarction as a time-dependent covariate, the predictive value of QRS duration was only marginally lower (QRS duration 100 to 119 ms vs. <85 ms; HR: 5.9; 95% CI: 2.2 to 15.8; $p < 0.001$). In this model, incident myocardial infarction was associated with a subsequent 4.6-fold higher risk of SCD (95% CI: 1.0 to 20.9; $p < 0.05$). One third of SCDs occurred in patients who had progressed to severe AS; distribution of AS severity before SCD in groups of baseline QRS duration and LBBB is given in Table 4. Of note, the average increase in QRS duration was ~1 ms per year, there was no detectable difference between patients randomized to the simvastatin/ezetimibe combination versus placebo (p = NS). Similarly, there was no difference in the risk of SCD between the 2 treatment arms (p = 0.98).

**Table 4** AS Severity Before Sudden Cardiac Death According to Baseline QRS Duration and LBBB*

| AS Severity | QRS <85 ms | QRS 85–99 ms | QRS 100–119 ms | LBBB |
|---|---|---|---|---|
| Mild AS | 1 (0.4)† | 2 (2.3)† | 1 (3.8)† | 1 (6.7)† |
| Moderate AS | 2 (0.5)† | 6 (3.4)† | 5 (7.5)† | — |
| Severe AS | 6 (2.2)† | 1 (0.8)† | 2 (3.9)† | — |

Values are n (%). Mild = peak aortic jet velocity >2.5 to <3.0 m/s; moderate; peak aortic jet velocity ≥3.0 to ≤4.0 m/s; severe = peak aortic jet velocity >4.0 m/s. *Last known value of peak aortic jet velocity before sudden cardiac death. †Incidence in the percentage of sudden cardiac deaths in the cells defined by QRS characteristics and aortic stenosis severity.
AS = aortic stenosis; LBBB = left bundle branch block.

**Prognostic value of QRS morphology in patients with BBB.** At baseline, a total of 102 patients had QRS duration ≥120 ms, including 43 (42.1%) with LBBB, 39 (38.2%) with isolated RBBB, and 20 (19.6%) with RBBB and left anterior fascicular block (left posterior fascicular block was not detected in patients with RBBB); 6 patients had QRS duration >140 ms and the widest QRS complex was 160 ms (n = 1). As shown in Table 5, there was no difference in major baseline characteristics between patients

**Table 5** Baseline Demographics and Echocardiographic Characteristics of Participants With RBBB

| Variable | RBBB (n = 39) | RBBB + LAFB (n = 20) | p Value |
|---|---|---|---|
| Age, yrs | 71.2 ± 3.0* | 72.2 ± 4.1* | 0.67 |
| Male, % | 82.1* | 90.0* | 0.39 |
| Peak aortic jet velocity, m/s | 3.25 ± 0.18 | 3.10 ± 0.24 | 0.34 |
| Aortic valve area/BSA, cm/m$^2$ | 0.60 ± 0.06 | 0.60 ± 0.08 | 0.97 |
| Left ventricular mass/BSA, g/m$^2$ | 104.6 ± 8.6* | 106.4 ± 11.4* | 0.84 |
| Left ventricular ejection fraction, % | 66.7 ± 2.6 | 65.3 ± 3.5 | 0.57 |
| Posterior wall thickness, cm | 0.93 ± 0.06* | 0.91 ± 0.08 | 0.83 |
| Left ventricular diastolic dimension, cm | 4.98 ± 0.20 | 5.17 ± 0.26 | 0.28 |
| Left ventricular systolic dimension, cm | 3.12 ± 0.17 | 3.30 ± 0.23 | 0.30 |
| Relative wall thickness, cm | 0.38 ± 0.03 | 0.36 ± 0.04 | 0.57 |
| Intraventricular septal thickness, cm | 1.23 ± 0.09* | 1.22 ± 0.11 | 0.95 |

Values are mean ± SD or %. *p < 0.05 compared with QRS duration <85 ms (Dunnett's test).
BSA = body surface area; LAFB = left anterior fascicular block; RBBB = right bundle branch block.

with RBBB alone or with left anterior fascicular block. The impact of LBBB is presented in Tables 2 and 3. In unadjusted analysis, patients with RBBB and left anterior fascicular block had, compared with those with QRS duration <85 ms, a 4.6-fold higher risk of myocardial infarction (95% CI: 1.1 to 19.5; p = 0.04). This association was nonsignificant in multivariable analysis (p = NS). There were no SCDs in RBBB with or without left anterior fascicular block. Compared with QRS duration <85 ms, isolated RBBB was not associated with an increased risk of any predefined endpoint.

## Discussion

This study is, to the best of our knowledge, the first to investigate the association of QRS duration with the risk of cardiovascular morbidity and mortality in a large contemporary population of asymptomatic patients with mild to moderate AS, and several of our findings add to current knowledge. First, longer QRS duration is associated with risks of SCD and overall cardiovascular death independent of clinical and echocardiographic covariates. Second, among patients with QRS duration ≥120 ms, only those with LBBB or combined RBBB and left anterior fascicular block have an increased risk of cardiovascular events.

Underlying mechanisms of SCD in relation to QRS duration in patients with chronic pressure load are uncertain but may reflect associations of increased QRS duration with: 1) adverse LV response to increased afterload above the changes in LV mass per se (20); 2) myocardial scarring due to chronic subendocardial ischemia and fibrosis (21), further supported by the association with incident myocardial infarction; and 3) a higher threshold for termination of spontaneously occurring ventricular tachycardia in the presence of longer QRS duration (22). The latter hypothesis is further supported by the fact that QRS morphology was, in patients with QRS duration ≥120 ms, more important for the risk of adverse outcome than that of QRS duration per se. On the molecular level, cardiac conduction velocity is affected by fibrosis, connexins, and ion channels, which, among other mechanisms, are influenced by activity in the renin-angiotensin system (23). Longer QRS duration could therefore be an early sign of subclinical cardiac damage, which may not be detectable by standard echocardiographic examination. However, we have not found any studies investigating the mechanism of QRS duration and risk of SCD in asymptomatic patients with AS. In patients with pressure overload due to hypertension, QRS duration has been shown to be independently predictive of SCD (4). AS symptoms and reduced LV systolic function were exclusion criteria in the current study. This adds to evidence that QRS duration and morphology are, independent of study population, associated with a poor prognosis and, in particular, the risk of SCD. Although differences in QRS duration could result from less than severe AS, baseline abnormalities may have had explanations other than AS. Indeed, this is quite likely, given the high prevalence of concomitant systemic hypertension in this population (24). In addition, the predictive value of QRS duration might have been different in AS patients with subclinical ischemic heart disease. However, even after adjusting by incident myocardial infarction and simvastatin/ezetimibe compared with placebo, QRS duration remained a highly significant predictor of SCD. Comparing the observed incidence of SCD with an age- and sex-matched U.S. background population (18), the rate of SCD in patients with QRS <85 ms seems to resemble that in individuals without AS.

The different outcome in LBBB compared with RBBB with and without left anterior fascicular block indicates first that isolated RBBB does not predict adverse events in patients with asymptomatic AS. Second, LBBB is not associated with a greater risk of cardiovascular events in patients with asymptomatic AS than moderate QRS prolongation alone. This concurs with recent data from the general population, suggesting that BBB is not as strong a predictor of arrhythmic death as prolonged QRS duration not meeting criteria for BBB (25). A potential pathophysiological mechanism may be that BBB reflects a disturbance in the conduction system, whereas longer QRS duration without BBB reflects abnormal depolarization in the myocardium itself.

**Study limitations.** In the SEAS population of asymptomatic patients with mild to moderate AS, relatively few patients had QRS duration ≥120 ms, which may reflect their exclusion from the study population due to symptom onset or death. The latter hypothesis is consistent with the increased rate of SCD associated with longer QRS duration in the present study. The exclusion of AS patients with symptoms, overt coronary artery disease, or previous heart failure resulted in relatively small numbers of SCDs and myocardial infarctions as well as small groups with LBBB or RBBB. The low number of events resulted in wide confidence intervals, the inability to build comprehensive multivariable analyses, and the risk of overfitted models. The relatively low power to determine independent predictors of hard endpoints should be kept in mind when interpreting our findings.

## Conclusions

In asymptomatic patients with AS, QRS duration is independently associated with the risk of SCD and overall cardiovascular death. Our findings suggest that QRS duration and morphology, as well as factors influencing these parameters, should be included when estimating the risk associated with watchful waiting and thus the need for intervention in asymptomatic AS. The fair prognosis associated with QRS <85 ms might suggest that early AVR is not likely to have a significant benefit in reducing SCD in these patients.

**Reprint requests and correspondence:** Dr. Anders M. Greve, Rigshospitalet, Department of Medicine B2142, The Heart Center, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark. E-mail: greve_anders@hotmail.com.

## REFERENCES

1. Carabello BA. Aortic stenosis: from pressure overload to heart failure. Heart Fail Clin 2006;2:435–42.
2. Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007;28:230–68.
3. Carabello BA. Evaluation and management of patients with aortic stenosis. Circulation 2002;105:1746–50.
4. Morin DP, Oikarinen L, Viitasalo M, et al. QRS duration predicts sudden cardiac death in hypertensive patients undergoing intensive medical therapy: the LIFE study. Eur Heart J 2009;30:2908–14.
5. Dhingra R, Pencina MJ, Wang TJ, et al. Electrocardiographic QRS duration and the risk of congestive heart failure: the Framingham Heart Study. Hypertension 2006;47:861–7.
6. Dhar R, Alsheikh-Ali AA, Estes NA 3rd, et al. Association of prolonged QRS duration with ventricular tachyarrhythmias and sudden cardiac death in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). Heart Rhythm 2008;5:807–13.
7. Dhingra R, Ho NB, Benjamin EJ, et al. Cross-sectional relations of electrocardiographic QRS duration to left ventricular dimensions: the Framingham Heart Study. J Am Coll Cardiol 2005;45:685–9.
8. Nair CK, Aronow WS, Stokke K, Mohiuddin SM, Thomson W, Sketch MH. Cardiac conduction defects in patients older than 60 years with aortic stenosis with and without mitral anular calcium. Am J Cardiol 1984;53:169–72.
9. Rossebo AB, Pedersen TR, Allen C, et al. Design and baseline characteristics of the simvastatin and ezetimibe in aortic stenosis (SEAS) study. Am J Cardiol 2007;99:970–3.
10. Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008;359:1343–56.
11. Greve AM, Gerdts E, Boman K, et al. Differences in cardiovascular risk profile between electrocardiographic hypertrophy versus strain in asymptomatic patients with aortic stenosis (from SEAS data). Am J Cardiol 2011;108:541–7.
12. Prineas RJ, Crowe RS, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings. Bristol: John Wright, 1982.
13. Cramariuc D, Cioffi G, Rieck AE, et al. Low-flow aortic stenosis in asymptomatic patients: valvular-arterial impedance and systolic function from the SEAS Substudy. J Am Coll Cardiol Img 2009;2:390–9.
14. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr 2009;10:1–25.
15. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
16. Fine JP, Gray RJ. A proportional hazard model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
17. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72.
18. Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol 2004;44:1268–75.
19. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). J Am Coll Cardiol 2004;43:1459–65.
20. Goldberger AL, Bhargava V. QRS duration measurement using high-frequency electrocardiography: applications and limitations of a new technique. Comput Biomed Res 1982;15:474–84.
21. Das MK, Suradi H, Maskoun W, et al. Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. Circ Arrhythm Electrophysiol 2008;1:258–68.
22. Nagai T, Kurita T, Satomi K, et al. QRS prolongation is associated with high defibrillation thresholds during cardioverter-defibrillator implantations in patients with hypertrophic cardiomyopathy. Circ J 2009;73:1028–32.
23. Kasi VS, Xiao HD, Shang LL, et al. Cardiac-restricted angiotensin-converting enzyme overexpression causes conduction defects and connexin dysregulation. Am J Physiol Heart Circ Physiol 2007;293:H182–92.
24. Rieck AE, Cramariuc D, Staal EM, Rossebo AB, Wachtell K, Gerdts E. Impact of hypertension on left ventricular structure in patients with asymptomatic aortic valve stenosis (a SEAS substudy). J Hypertens 2010;28:377–83.
25. Aro AL, Anttonen O, Tikkanen JT, et al. Intraventricular conduction delay in a standard 12-lead electrocardiogram as a predictor of mortality in the general population. Circ Arrhythm Electrophysiol 2011;4:705–10.

**Key Words:** asymptomatic aortic stenosis ■ QRS duration ■ sudden cardiac death.